

SOME DIFFICULT TOPICS TO TEACH (AND NOT TO TEACH) IN RENAL PHYSIOLOGY

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This paper deals with the teaching of various unrelated topics. Several I have found to be difficult to teach or likely not to be covered at all because of the way that our presentation of renal physiology is usually organized. Several have been chosen to raise questions about how (and what) to teach at this time of unprecedented explosion of knowledge. The general topics chosen for review are 1) interactions of systems controlling the excretion of specific substances; 2) how vasoactive substances lower or raise glomerular filtration rate (GFR); 3) urea and urine concentration; and 4) feedbacks and bottom lines: "So what really happens?"

TOPIC 1: INTERACTIONS OF SYSTEMS CONTROLLING THE EXCRETION OF SPECIFIC SUBSTANCES

Usually, in our teaching, we describe, one at a time, how the excretion of specific substances is homeostatically controlled. But, for normal physiology and pathophysiology, it is also important to point out some of the interactions between these individual systems. Certainly, when I do not do this, there are always a few good students who see the potential problems and question me about them. These students see, first of all, that tubular transport proteins often function as co- and countertransporters, that the paracellular pathway for all substances depends on water reabsorption and electrical potential differences, variables influenced by multiple ions. And, finally, they see that primary controlling inputs, like aldosterone, almost always influence the renal handling of more than one substance. I would like to focus on this last category because it often "falls between the cracks" in the descriptions devoted to single substances.

Such interactions can be framed by two broad statements: 1) During the homeostatic regulation of one

ion, events occur that can potentially cause inappropriate changes in the excretion of another ion; and 2) there often exist mechanisms for preventing these inappropriate changes. I give three important examples.

The first example concerns antidiuretic hormone (ADH) and potassium secretion (Fig. 1). Recall from Dr. Knox's presentation (3) that potassium secretion is increased when flow through the cortical collecting duct is increased. Because water diuresis increases flow through the cortical collecting duct, it should cause an increased potassium secretion and excretion. Yet, such an increase generally does not occur. The explanation is that ADH itself directly stimulates potassium secretion by the cortical collecting duct. The reduction in plasma ADH associated with water loading removes a portion of the direct stimulation normally exerted by higher plasma ADH, and this causes a decrease in potassium secretion. This decrease in secretion tends to cancel out the increased secretion caused by the increased flow.

For water deprivation, just reverse all the arrows. Water deprivation causes an increase in ADH, which does two opposing things that cancel each other out: it indirectly reduces potassium secretion by lowering flow through the cortical collecting duct, but it simultaneously stimulates potassium secretion by a direct tubular effect.

My second example can be phrased as the following question: Why doesn't a primary sodium imbalance cause a renally induced potassium imbalance (Fig. 2)? The problem here, of course, is that aldosterone controls the renal excretion of both sodium and potassium; therefore, when sodium deprivation stimulates aldosterone secretion, the increased plasma aldosterone will stimulate not only sodium reabsorption,

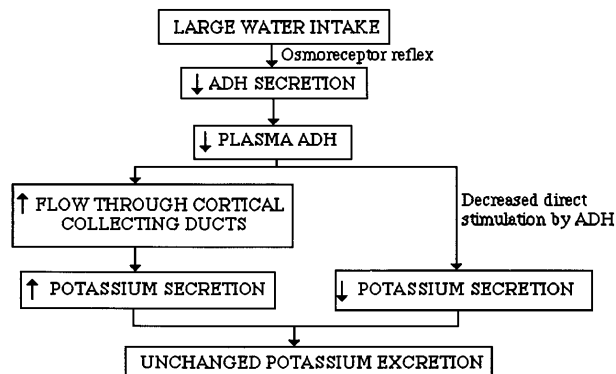


FIG. 1.

Lack of increased potassium excretion during water diuresis: opposing effects of decreased antidiuretic hormone (ADH) and increased cortical collecting duct flow on potassium secretion.

the “desired” homeostatic effect, but also potassium secretion. The expected result should be increased potassium excretion and a negative potassium balance, but this does not usually occur during sodium deprivation. Once again, the reason is the flow dependence of potassium secretion in the cortical collecting duct. Sodium deprivation causes a decrease in GFR and an increase in proximal sodium reabsorption, and so there is a decreased fluid delivery to the cortical collecting duct. This reduces potassium secretion. The flow effect and the aldosterone effect tend to cancel each other out, and the result is a relatively unchanged potassium secretion and excretion. This same balancing act occurs when a rise in aldosterone is caused by heart failure or any of the other syn-

dromes associated with secondary hyperaldosteronism.

By the same logic, a person on a high-sodium diet usually has a normal potassium excretion [unless he or she is being given diuretics at the same time (3)]. Again, just reverse the arrows—during a high-sodium diet aldosterone is low and collecting duct flow is high—the opposing effects of these changes on potassium secretion pretty much cancel each other out.

The next example is the opposite side of the coin from the previous one: Why doesn’t a primary potassium imbalance cause a renally induced sodium imbalance via aldosterone? As shown in Fig. 3, a high-potassium diet stimulates aldosterone secretion, and the increased aldosterone stimulates sodium reabsorption, which should produce inappropriate sodium retention. This does not usually occur, however. The explanation is that an increased plasma potassium concentration acts directly on the proximal tubule to inhibit sodium reabsorption (the mechanism is presently unclear). This decreased proximal reabsorption of sodium tends to cancel out the aldosterone-induced increased reabsorption by the cortical collecting duct, and sodium excretion does not change.

I would like to emphasize that the three interactions I have described here are, in a sense, “anticipatory” adaptations; that is, they prevent an imbalance from occurring. My guess is that many anticipatory interactions other than those I have presented occur. For

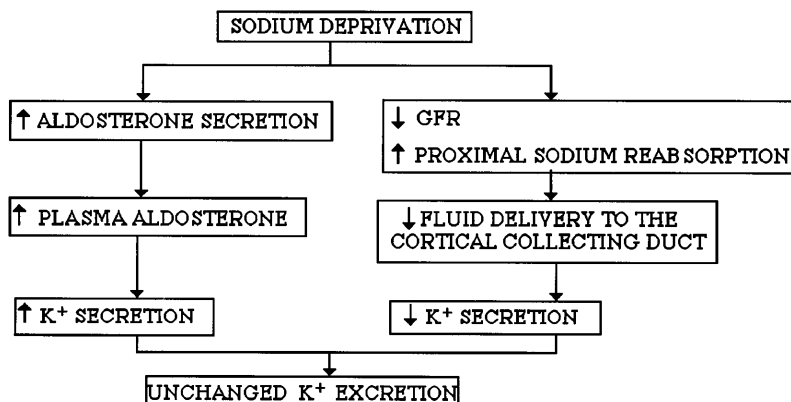


FIG. 2.

Lack of increased potassium excretion during sodium deprivation: opposing effects of increased aldosterone and decreased cortical collecting duct flow on potassium secretion. GFR, glomerular filtration rate.

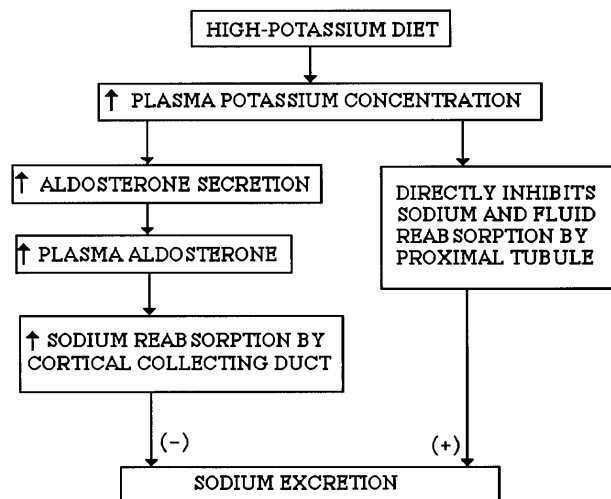


FIG. 3.

Lack of increased sodium excretion during ingestion of a high-potassium diet: opposing effects of increased aldosterone and increased plasma potassium on sodium reabsorption.

example, someone needs to work out the significance, in this regard, of the interactions among parathyroid hormone, calcium reabsorption, and sodium reabsorption. Here we have another hormone that influences the excretion of more than one ion.

Of course, there really are times when such adaptive modulating factors either do not exist or are not successful in preventing the regulation of one ion from causing the kidneys to excrete too much or too little of another. A very important clinical example of

this is that the presence of extracellular volume contraction interferes with the ability of the kidneys to compensate for a simultaneously existing metabolic alkalosis. The major reason is that both angiotensin II and aldosterone are homeostatically elevated by extracellular volume contraction, and as noted by Dr. Koeppen in his presentation (4), these two hormones stimulate the tubular secretion of hydrogen ions. However, such stimulation is maladaptive for response to an alkalosis, a situation calling for the kidneys to excrete bicarbonate. This is why the kidneys fail to compensate for the alkalosis.

When I tell my students this, they are irritated by what seems like a bizarre coincidence; it makes no sense to them that these two sodium-retaining hormones should also stimulate hydrogen ion secretion. So, I have finally convinced myself that it is important to present to them the additional material needed to see the logic. It is that aldosterone and angiotensin II have another physiological function; they participate in a homeostatic control system that regulates plasma hydrogen ion concentration. This reflex is shown in Fig. 4. Acidosis stimulates the secretion of renin, which leads, via angiotensin II, to the stimulation of aldosterone secretion. In addition, acidosis acts directly on the adrenal cortex to stimulate aldosterone secretion. Both angiotensin II and aldosterone then stimulate hydrogen ion secretion. The result is an increase in bicarbonate reabsorption and hydrogen ion excretion, which alkalinizes the blood. Thus the ability of angiotensin II and aldosterone to stimulate

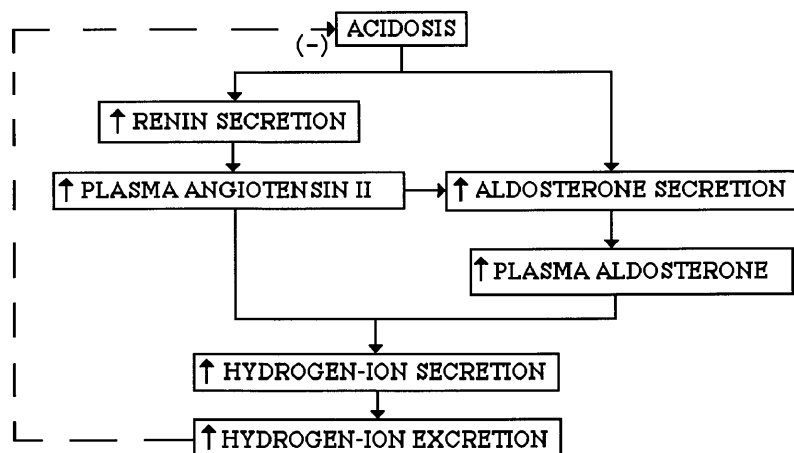


FIG. 4.

Homeostatic role of aldosterone and angiotensin II in acidosis.

hydrogen ion secretion is not a bizarre coincidence but is an integral part of a negative-feedback system for regulating plasma hydrogen ion concentration.

Now, apply this to alkalosis. A homeostatic response for restoring acid-base balance would be to reduce the secretion of renin and aldosterone, and this probably occurs if all other factors remain unchanged. The problem occurs when extracellular volume contraction also exists, for this is a major stimulus for secretion of renin and aldosterone, much stronger than any tendency for alkalosis to inhibit their secretion. In other words, when the secretion of these two hormones is stimulated by extracellular volume contraction rather than lowered blood pH, the resulting stimulation of hydrogen ion secretion by the kidneys is maladaptive, not homeostatic.

TOPIC 2. HOW VASOACTIVE SUBSTANCES LOWER OR RAISE GFR

My experience is that most students, at least initially, believe that vasoactive substances, including the neurotransmitter norepinephrine, influence GFR by altering the glomerular capillary hydrostatic pressure (P_{gc})—specifically, that vasoconstrictors lower this

pressure and vasodilators raise it. Now, this explanation may be correct in the case of marked vasoconstriction or vasodilation, but it is not correct for most physiological situations. In reality, P_{gc} very often goes in the wrong direction to account for the GFR change.

This point is illustrated in Fig. 5, which summarizes the effects of most vasoconstrictors on the factors that determine GFR. There are quantitative differences among the various vasoconstrictors (for example, angiotensin II vs. norepinephrine), but most constrict both the afferent and efferent arterioles. Because of the opposing effects of this afferent and efferent constriction, P_{gc} may go up or down or remain unchanged. In animal experiments, the most common response is a small increase. But, regardless of what happens to P_{gc} , net filtration pressure always goes down, mainly because of an increase in average glomerular capillary colloid osmotic pressure (π_{gc}). This change is itself the result of a decrease in renal plasma flow (RPF). In addition, most vasoconstrictors cause a decrease in glomerular filtration coefficient (K_f), which contributes to the lowering of GFR.

Admittedly, learning how to construct a figure like this is a lot of work for a student, and my own bias is that it

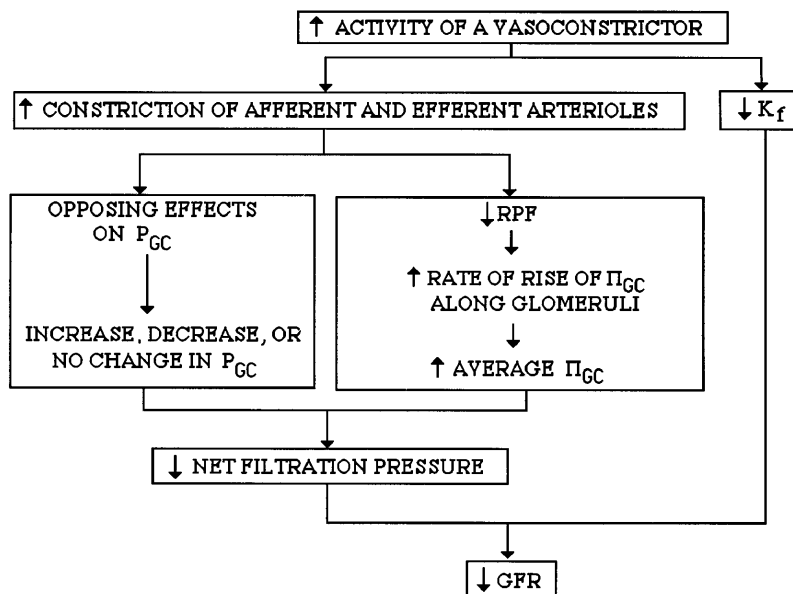


FIG. 5.

Mechanisms by which vasoconstrictors cause a reduction in GFR. K_f , glomerular filtration coefficient; P_{gc} , glomerular capillary hydrostatic pressure; π_{gc} , glomerular capillary colloid osmotic pressure.

is overkill for students other than medical students. For all those students, it ought to be enough simply for them to know that vasoconstrictors and vasodilators tend to lower and raise GFR, respectively. (This is in keeping with one of my major teaching rules—you should never lie but you don't need to tell the entire truth.) However, this is such an important clinical area that it is worth expending the effort to have medical students learn how to construct accurate models.

Part of the problem, I believe, is that the students apply, incorrectly, what they have learned earlier in their physiology course about the microcirculation to the more complex glomerular situation. Pointing out to them the specific differences is a good teaching approach, and I do this, using Fig. 6 as a guide. In this figure, a solid line denotes a positive relationship and a dashed line an inverse one. For example, an increase in afferent arteriolar resistance (R_a) causes a decrease in P_{gc} .

The first and most obvious problem is that the students earlier have learned the relationship between arteriolar resistance and capillary hydrostatic pressure in the context of a single set of arterioles proximal to the capillaries. Now they must incorporate into their thinking two sets of arterioles and the fact that when R_a and efferent arteriolar resistance (R_e) both change in the same direction the changes have opposing effects on P_{gc} . In contrast, such changes have additive effects on renal blood flow (RBF). This dichotomy between the effects of the two resistances on GFR and RBF must be emphasized as strongly as possible.

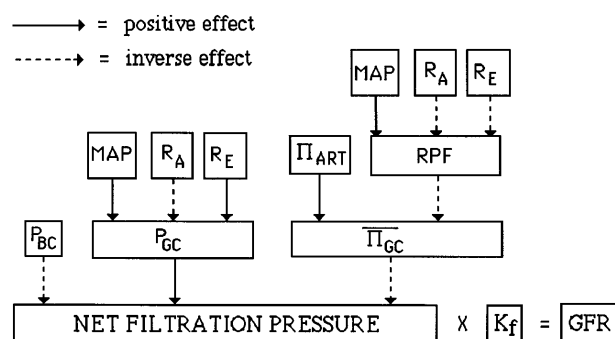


FIG. 6.

Factors that determine GFR. MAP, mean arterial blood pressure; R_a , afferent arteriolar resistance; R_e , efferent arteriolar resistance; π_{art} , arterial colloid osmotic pressure.

Second, the students have learned for the other capillary beds to use simply the arterial colloid osmotic pressure (π_{art}) as the capillary colloid osmotic pressure. This is valid because the capillary colloid osmotic pressure does not change significantly along the length of other capillaries in the body, because so little of the plasma is filtered. Now they must recognize that this is not the case for the glomerular capillaries. π_{gc} at the beginning of the glomerular capillaries is, of course, equal to π_{art} , but because such a large fraction of the RPF is filtered, π_{gc} increases a good deal along the length of the glomerular capillaries. Now comes the most important fact to emphasize: All other factors remaining constant, the rate of rise of π_{gc} along the capillaries, and hence the average π_{gc} , is inversely dependent on the RPF (that is, the higher the plasma flow, the lower the rate of rise). It is not hard for the students to visualize that the filtration of a given volume of fluid from a small total volume of plasma flowing through the glomeruli will cause the protein left behind to become more concentrated than if the RPF were large.

A word of advice about semantics: It is very important when we list the determinants of GFR to clearly distinguish the direct determinants, like average π_{gc} , from the indirect determinants, like RPF. If you simply give RPF in a list of determinants of GFR, the student gets the idea that RPF acts somehow by a mechanism different from the basic Starling capillary forces. That is why, in this figure, I place the direct and indirect determinants at different levels. This is all so obvious to us that we forget how confused students can become in tracing chains of causality.

Third, during their study of cardiovascular physiology, students are told that capillary filtration coefficients do not usually change under physiological conditions. Again, this is not true for the glomerular capillaries because many of the vasoactive agents operating in normal physiological reflexes cause glomerular K_f to change, mainly by constricting or dilating the glomerular mesangial cells. So, K_f must always be considered, in addition to net filtration pressure.

A final problem in teaching and learning these basic principles is not what the students have previously learned, but rather the uncertainties we, as instructors, have in quantitating the importance of some of

the variables. These uncertainties stem largely from the fact that the influences of RPF and K_f vary, depending on whether filtration equilibrium is reached in the glomerular capillaries. [I will not detail the reasons here, but a beautiful analysis is presented in the cited review by Arendshorst and Navar (1)]. I think this topic is well beyond what we want our students to have to deal with, and I recommend not even raising the question but simply stating that, for several reasons, one should think of changes in these variables as “tending” to change GFR, without worrying about quantification.

TOPIC 3. UREA AND URINE CONCENTRATION

Urea has an important role in determining the maximal urinary osmolality, one that is well established and quite easy to understand. This role, however, is often obscured in our description of another, hypothesized role for urea in urinary concentration.

The facts basic to both these roles are as follows. During antidiuresis, as fluid flows through the cortical collecting ducts and outer medullary collecting ducts, luminal urea concentration rises progressively and markedly. This occurs because water is reabsorbed in these ADH-sensitive segments but urea is not, because these segments are essentially impermeable to urea. In contrast, the inner medullary collecting ducts have facilitated-diffusion transporters for urea, which are ADH activated; as fluid flows through this segment, therefore, urea is reabsorbed, driven by the high urea concentration established in the preceding segments. The net result is that the urea concentration of the inner medullary interstitial fluid comes to approximate the urea concentration of the luminal fluid within adjacent inner medullary collecting ducts. In essence, then, urea within the tubule is balanced by urea outside the tubule.

Typical values for antidiuresis are shown in Table 1. Maximal urine osmolality is 1,400 mosmol/l, and about one-half of this is urea. Because the urea in the interstitium balances itself, the sodium and chloride concentrations established in the interstitium by the countercurrent multiplier system need balance only solutes other than urea in the tubular fluid. If there were no urea in the interstitial fluid, the medullary interstitial osmolality contributed by sodium and chloride would have to be the full 1,400 rather than 750

TABLE 1
Composition of medullary interstitial fluid and urine during antidiuresis

Interstitial Fluid at Tip of Medulla, mosmol/l	Urine, mosmol/l
Urea = 650 $\text{Na}^+ + \text{Cl}^- = 750$	Urea = 700 Nonurea solutes = 700 (Na^+ , Cl^- , K^+ , urate, creatinine, etc.)

mosmol/l. To achieve that, more sodium chloride would have to be transported by the ascending limbs of Henle's loop. To reemphasize, in this description so far, urea plays no role in establishing a countercurrent gradient, nor does it cause water to move out of the collecting ducts; it merely balances itself and, in so doing, increases the maximal urinary concentration achievable.

Now let us look at the second potential role for this interstitial urea. More than 25 years ago it was hypothesized that this urea is involved in the actual creation of the countercurrent multiplier gradient for sodium chloride. This elegant hypothesis, known as the “passive model,” was designed to explain a problem that has always bedeviled the field, namely the fact (or at least the strong likelihood) that, unlike the thick ascending limb, the thin ascending limb does not actively reabsorb sodium chloride. Because the thin limb is the only part of the loop that extends into the inner medulla, how, then, can the inner medulla participate in creating the countercurrent gradient there? It is not my goal to analyze the passive model (see Ref. 2) but only to point out that it invokes a special role for interstitial urea in causing water and sodium chloride movement out of the thin limb. Even today, there is no consensus as to the correctness of this hypothesis (or any of the competing theories). As Knepper and Rector have stated in their superb recent review (2), “All of the models appear to have either theoretic drawbacks or discrepancies between the quantitative requirements of the model and the actual experimental observations.”

In other words, we simply do not really know how the inner medulla functions in the countercurrent multiplier system. My own teaching approach is to present the functioning of the thick ascending loop, point out the problem of what causes sodium chloride transport in the inner medulla, and state that we presently do

not have an answer to the problem. If you prefer to present the passive model [for example, see Dr. Schafer's presentation in this issue (5)], I would urge you to make certain that the well-established and quite distinct function for interstitial urea that I described earlier does not become left out or obscured in the process.

This raises the much larger issue, which I hope we will talk about in the discussion period, of how we choose what to teach and not to teach. I do not think that difficulty alone should be a major criterion; when a crucial basic principle such as the determinants of glomerular filtration is involved, we should spare no effort in presenting it and making it clear. But I also think that we should not be shy in admitting when an answer is not yet known, and we should be very careful about burdening the student with hypothetical explanations, particularly when they are quite complex or multiple. Another example that comes to mind in this regard is trying to explain what causes potassium excretion to change in chronic acidosis; here again, I think the best approach is to tell the student that, in contrast to the alkalosis-potassium story, no simple generalization applies to the effects of acidosis on potassium excretion and let it go at that.

TOPIC 4. FEEDBACKS AND BOTTOM LINES: "SO, WHAT REALLY HAPPENS?"

This topic is concerned with how to deal with certain aspects of complexity in our teaching. To introduce it, I would like quote from a letter I received several years ago: "I am curious about some bottom lines in real-life situations. I have learned about autoregulation of RBF and GFR, glomerulotubular balance, tubuloglomerular feedback, a zillion effects of sympathetic nerves, angiotensin II, aldosterone, and da, da, da. Many of the things I have learned seem to work in opposite directions. So what really happens to RBF, GFR, sodium, and free water excretion when someone exercises, is confined to bed, stands up, drinks a beer, eats something salty, is being treated with diuretics, etc?"

The person who wrote this letter is a very experienced and excellent teacher and textbook writer. He had just finished teaching renal physiology, not his specialty, for the first time. He has a strong background in engineering and control systems, and the

Primary inputs controlling RBF

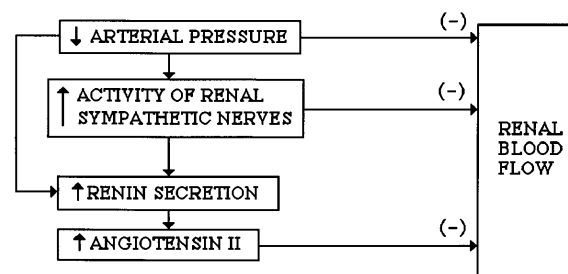


FIG. 7.

Primary inputs lowering renal blood flow (RBF) in response to a reduction in arterial pressure.

letter was not a request for information but was largely a plea to think about how confused our students can be in the face of all the feedback loops and mechanisms we pile on them.

So, how do we handle this? I would like to suggest one approach, that we present the material in layers, the first layer being the absolutely essential primary inputs, along with the bottom line. Depending on the students we are teaching, that may be all we want them to learn. In any case, as we add more layers we should keep referring back to the primary inputs and the bottom line. Let me take one example, control of RBF during a hemorrhage that has produced mild hypotension. Let me emphasize that my aim is to use this as a tool, not to review systematically the control of RBF. The same logic approach would apply to any endpoint, for example sodium excretion in a person on a high-salt diet.

Primary inputs plus two modulating factors

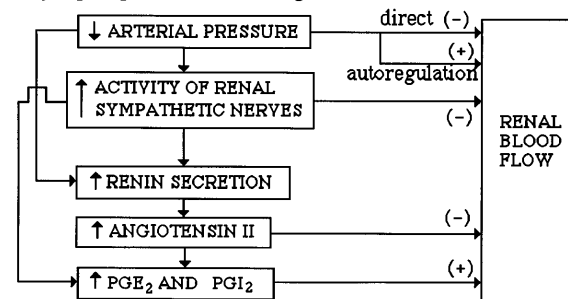


FIG. 8.

Role of autoregulation and prostaglandins in minimizing the decrease in RBF that occurs in response to a reduction in arterial blood pressure. PGE₂, prostaglandin E₂; PGI₂, prostacyclin.

Feedbacks among neurochemical inputs

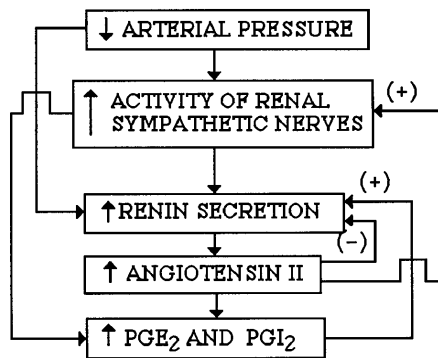


FIG. 9.
Positive and negative feedbacks among primary inputs controlling RBF.

The first figure (Fig. 7) illustrates what I mean by the primary inputs to the kidneys—in this case, arterial pressure, the renal sympathetic nerves, and angiotensin II. This figure should make it absolutely clear to the student that this situation will cause a decrease in RBF, because all the inputs are driving RBF in that direction, as indicated by the minus signs.

The next figure (Fig. 8) adds two well-known counteracting effects, which tend to minimize (negatively modulate) the decrease in RBF: autoregulation and release of the vasodilator prostaglandins. If you emphasize that such modulating effects in physiology do not usually completely overcome the effects of the primary inputs that elicit them, the student should recognize that the bottom line is still a decrease in RBF.

TABLE 2
Renal paracrine (excluding cytokines and growth factors)

Vasodilators: Nitric oxide, dopamine, kinins, adrenomedullin, PGE ₂ , and PGI ₂
Vasoconstrictors: Endothelin, angiotensin II, thromboxane A ₂ , leukotrienes
Mixed effects: Adenosine, urodilatin

PGE₂, prostaglandin E₂; PGI₂, prostaglandin I₂.

The layer I just added describes modulating factors that act directly on the arterioles, that is, on the effectors in this reflex response. There is quite a different type of modulation, namely, feedbacks that act on the primary inputs themselves. This layer is shown in the next figure (Fig. 9). You can see that there are two positive feedbacks and one negative. Do you want the students to know any or all of these? If your answer is yes, recognize that you are asking them to know Fig. 10. Until I constructed this figure for this presentation, I had never appreciated how the small amounts of information we may present to students at different times accumulate rapidly to scary proportions. Making such figures just for your own use is, therefore, a good exercise.

Also, keep in mind that the situation is rapidly worsening, for the paracrine are coming, the paracrine are coming! These locally acting intrarenal substances are one of the most exciting fields in renal physiology today, and several of the presentations in this refresher course describe this important and fascinating information. But the abundance of information poses real problems for the teacher and student. For example, Table 2 presents a partial list of some of the

Amalgamation of previous figures

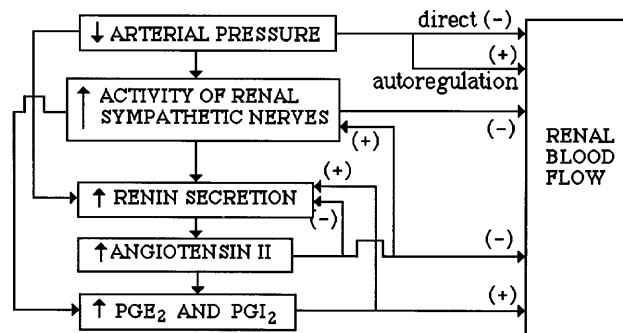


FIG. 10.
An amalgamation of Figs. 8–10.

renal paracrine and their effects on the renal arterioles (I have left out the many renal growth factors and cytokines). Keep in mind that some of these paracrine may mediate the effects of the primary inputs; for example, it is likely that nitric oxide is a major mediator of pressure natriuresis. Other paracrine may modulate the primary inputs, either positively or negatively; for example, ADH stimulates the secretion of prostaglandins, which then oppose some of the effects of ADH on the collecting duct. Moreover, there are almost certainly multiple negative and positive feedback loops among the paracrine themselves.

We surely cannot teach more than a fraction of all this information, even though much of it is (or will become) clinically relevant. Keep in mind that the same explosion of information is occurring in the areas of the receptors, signal transduction pathways, channels, and transporters influenced by all these messengers. One solution is to provide the students with tables such as this, but stress that the information is for reference only and that any students caught

memorizing it will be shot at dawn. When you come to actually make your decisions, just remember that our students are already having troubles keeping track of the single most important question: "So, what really happens?"

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